METHODS AND COMPOSITIONS FOR TREATING A RESPIRATORY DISEASE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 63/011,521 filed on Apr. 17, 2020, the contents of which is incorporated herein by reference in its entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Apr. 15, 2021, is named 002806-093130USPT_SL.txt and is 63,341 bytes in size.

TECHNICAL FIELD

[0003] The technology described herein relates to methods of making a lung surfactant, treating a respiratory disease, and uses thereof.

BACKGROUND

[0004] Respiration is a key component of human life. The lungs remove oxygen from air for transport via the blood stream to the entire body. surfactant B protein (SP-B) is a surfactant essential for breathing in mice and humans. It is made in alveolar type II cells as a precursor containing three domains related to the lysosome-localized saposins. The precursor is proteolytically processed into the individual domains, with the middle domain (SP-BM) currently considered to be the biologically important "mature" protein. SP-BM is initially stored in lamellar bodies (LB), lysosome-like organelles, in which membrane sheets are densely stacked on top of each other. LBs are eventually exocytosed to generate extracellular surfactant, a mixture of phospholipids and protein. While surfactants derived from animals are available commercially, the surfactant mixture has proven to be ineffective in adults that suffer from respiratory diseases. Furthermore, generating SP-BM recombinantly has been a challenge in the industry and improved methods of manufacturing surfactants are needed.

SUMMARY

[0005] The methods and compositions provided herein are based in part, on the discovery that the domains of surfactant B protein (SP-B) each function in lamellar body (LB) formation and that the SP-BM domain alone can be expressed and purified to generate LB-like structures.

[0006] In one aspect, provided herein is a lung surfactant composition comprising:

[0007] a. a polypeptide comprising a surfactant B protein N-terminal domain (SP-BN); and

[0008] b. at least one phospholipid

[0009] In another aspect, provided herein is a lung surfactant composition comprising:

[0010] a. a polypeptide comprising a surfactant B protein middle domain (SP-BM); and

[0011] b. at least one phospholipid

[0012] In another aspect, provided herein is a method of treating a respiratory disease in a subject, the method comprising: administering to a subject in need thereof a lung surfactant composition provided herein.

[0013] In another aspect, provided herein is a method of treating a respiratory disease in a subject, the method comprises: administering through the trachea a composition or a vector encoding a polypeptide provided herein to a subject in need thereof.

[0014] In another aspect, provided herein is a vector comprising a nucleic acid sequence encoding SP-BM; SP-BN; or SP-BM and SP-BN.

[0015] In one embodiment of any of the aspects, the polypeptide provided herein further comprises a surfactant B protein N-terminal domain (SP-BN), and/or a surfactant B protein middle domain (SP-BM), and/or a surfactant B protein C-terminal domain (SP-BC), or any combination thereof. In another embodiment of any of the aspects, the polypeptide is a human, bovine, or mouse polypeptide. In another embodiment of any of the aspects, the SP-BN is human, bovine, or mouse SP-BN. In another embodiment of any of the aspects, the SP-BM is human, bovine, or mouse SP-BM.

[0016] In another embodiment of any of the aspects, the SP-BM comprises a cysteine (C, Cys) to alanine (A, Ala) amino acid substitution at position 48 (C48A). In another embodiment of any of the aspects, the SP-BN comprises a lysine to glutamic acid to glutamine (K46E) amino acid substitution at position 46, a proline to cysteine (P50C) amino acid substitution at position 50, an arginine to glutamine (R51E) amino acid substitution at position 51, a tyrosine to alanine (Y59A) amino acid substitution at position 59, and/or a histidine to alanine (H79A) amino acid substitution, or any combination thereof.

[0017] In another embodiment of any of the aspects, the phospholipid is a glycerophospholipid. In another embodiment of any of the aspects, the phospholipid is selected from the group consisting of: 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC); phosphatidylglycerol (PG); phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), and phosphatidylinositol (PI). In another embodiment of any of the aspects, the lung surfactant composition further comprises DPPC, PG, or a combination thereof.

[0018] In another embodiment of any of the aspects, the composition is formulated with a pharmaceutically acceptable carrier. In another embodiment of any of the aspects, the lung surfactant composition is formulated for intratracheal delivery.

[0019] In another embodiment of any of the aspects, the lung surfactant composition further comprises a Surfactant Protein C (SP-C) or a functional fragment thereof. In another embodiment of any of the aspects, the lung surfactant composition further comprises an additional lung surfactant.

[0020] In another embodiment of any of the aspects, the subject is a mammal. In another embodiment of any of the aspects, the subject is a human. In another embodiment of any of the aspects, the subject has or is suspected of having a respiratory disease.

[0021] In another embodiment of any of the aspects, the respiratory disease is selected from the group consisting of: acute respiratory distress syndrome (ARDS), neonatal respiratory distress syndrome (NRDS), pneumonia, asthma, meconium aspiration syndrome, respiratory failure, chronic obstructive pulmonary disease (COPD), and a lung infection.